CASAC Statistical Comments on Kim et al., *Lung function and inflammatory responses in health young adults exposed to 0.06 ppm ozone for 6.6 hours,* AJRCCM 183: 1215-1221 (2011)

I am a practicing Accredited Professional Statistician and I am making a few specific comments on the Kim et al., paper dealing with Lung function and inflammatory responses that appeared in the *American Journal of Respiratory and Critical Care Medicine*.

The data used in the analysis is a subset of the data collected for the original study. The data reported in the journal measured 59 subjects at two time points (at zero and 6.6 hours) and two levels of ozone, 0 ppb (clean air) and 60 ppb ozone. The full study measured the subjects at 5 time points, 0, 3.0, 4.6, 5.6 and 6.6 hours. Additionally, 30 of the 59 subjects were also measured at an exposure of 80 ppb ozone at these time points and 35 subjects at 18 hours post-exposure. The result is that the original study had 775 duration-exposure measurement points, but only 118 points (15 percent) were analyzed in the Kim et al. paper and the omitted data have a bearing on the interpretation of the study.

I obtained the more complete 740 point data set (absent the 18 hour post-exposure points) and analyzed it using the statistical methods noted by Kim et al. using FEV_1 and FVC as the dependent measures. Several model forms were used in my analyses. One option had the response as the difference between O_3 exposed and baseline, the other as a ratio; anther option included or excluded the 80 ppb exposure data; the third option considered two forms of the covariance matrix for the mixed models.

My analyses indicate that the statistical significance of the 60 ppb exposure for the FEV_1 response depended on the model used. The ratio measure was statistically significant whereas the difference measure was not. The estimated FEV_1 response to 60 ppb O_3 was a decrement of 1.2-1.8% where Kim et al reported a 1.7% decrement (their Table 3).

A decrement in FEV_1 of 1.7% should not be considered adverse in light of current guidelines (most authorities require a 12–15% increase in FEV_1 and/or FVC to define a meaningful response; changes 8% are likely to be within measurement variability). [1] Indeed, the variability in FEV_1 among people is illustrated by the subject's responses: one subject had an FEV_1 decrement of 16.4% after 6.6 hours of 60 ppb ozone exposure, but another had a 17.7% *increment* after 6.6 hours of filtered air exposure. In the Kim et al data set 22 of the 59 subjects, one third, show an FEV_1 *gain* from baseline at 6.6 hours when exposed to 60 ppb O_3.

Two messages emerge from these analyses. First, the statistical significance of the FEV_1 decrement following ozone exposure is dependent on the statistical analysis, which

[1] Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, et al. Interpretative strategies for lung function tests. Eur Respir J 2005; 26:948–968.

implies it may be an artifactual result. Second, regardless of the statistical significance, the observed responses are not physically detrimental or clinically meaningful and therefore do not support a causal effect at the 60 ppb ozone exposure level.

The Kim et al journal article indicates that "Linear mixed-effects models with a subject-specific random intercept was used to test changes in response endpoints between clean air and ozone exposures at the group level to account for subject-level variability and repeated measures." This is the analysis presented here for the full data set. The analysis done reported by Kim et al. on only the initial and final time points for only two dose groups is a two-sample t-test on the difference scores. It may be that the initial mixed-effects data analysis protocol was developed to analyze the full data set but in the end only the subset findings were reported. Similar points can be made about the FVC measures.

In conclusion, (1) the subset analyses reported in the Journal article is weaker than one using the full data set that was collected and (2) the statistical significance of the 60 ppb exposure group response depends on the statistical method of analysis. While the Kim et al. article notes that "This study reports that acute exposure to ozone for 6.6 hours at a level of 60 ppb causes significant effects on pulmonary function and airway inflammation in healthy young adults," it should indicate that the effect may be *statistically* significant and that the FEV_1 differences are not considered clinically significant, even for subjects undergoing strenuous quasi-continuous exercise over the 6.6-hour exposure period.

Thank you for your time and consideration.

Mark Nicolich, PhD
Statistician
COGIMET
24 Lakeview Rd
Lambertville, NJ 08530

mark.nicolich@gmail.com
609.397.4089